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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/460,292	12/10/1999	David J. Mangelsdorf	UTSD:596	2313

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EXAMINER	
WOITACH, JOSEPH T	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 12/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/460,292	Mangelsdorf et al.
Examiner	**Art Unit**
Joseph Woitach	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 28, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 4-14, 21, 23-27, 29, 44, and 45* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-14, 21, 23-27, 29, 44, and 45* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on August 28, 2002 has been entered.

DETAILED ACTION

This application is an original application filed December 10, 1999, which claims benefit to provisional application 60/111,894, filed December 10, 1998.

As indicated in Applicants' request for continued examination, Applicants amendment filed March 28, 2002, paper number 22, has been entered. The specification has been amended. Claims 1, 2, 4, 5, 21, 23, 26, 27, 44 and 45 have been amended. Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are pending and currently under examination.

Inventorship-Declaration filed under 37 CFR 1.48(a)

As noted in the advisory action mailed June 13, 2002, paper number 23 (section 5(a)), the petition to correct the inventorship filed February 15, 2002, paper number 21, has been accepted.

Declaration filed under 37 CFR 1.132

The Declaration of David Mangelsdorf under 37 CFR 1.132 filed June 6, 2001, paper number 14, is sufficient to overcome the rejection of claims 1-9, 14, 21-29, 44 and 45 based upon the 35 USC 102(a) rejection as anticipated by Peet *et al.*

The declaration under 37 CFR 1.48(a) is now properly filed. The change to the named inventors of the instant application has been entered. In view of the amendment to the inventorship and in light of the Declaration of David Mangelsdorf it is found that the Peet *et al.* does not represent a teaching by another.

Claim Objections

Claim 11 is objected to because of the following informalities: claim 11 has been amended and recites "region of the LXRα**s**" however it is believed that the claim should reflect the language of claim 10 reciting "LXRα ***gene***".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 10-14, 21, 23-27, 29, 44 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a disruption of the endogenous nuclear oxysterol receptor gene (LXRα), wherein said disruption in said mouse results in the decrease of the LXRα protein and said mouse exhibits hepatomegaly and cholesterol accumulation, does not reasonably provide enablement for transgenic mouse which comprises at least on endogenous LXRα allele that lacks the capacity to respond to dietary cholesterol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants indicate that the rejection appears to be directed to the embodiment of generating a transgenic mouse comprising a dominant negative heterologous gene, and argue that this constitutes an improper grounds for rejection because one can always envision some non-enabling situations. Further, Applicants note that Examiner acknowledges that a disruption in the LXRα allele is enabled, and indicate that upon review of the pending claims they believe that is what is being claimed. In light of the language of the pending claims, Applicants argue that the specification need not provide discussion of dominant negative mutants. See Applicants' amendment, pages 7-8. Applicants amendment has been fully considered but, not found persuasive.

As set forth in the basis of the scope of enablement rejection, Examiner would agree that a disruption in the LXRα allele that results in decreased levels of LXRα protein expression

wherein the knock-out mouse is incapable of responding to dietary cholesterol is fully enabled. Accordingly, claims 4-9 encompassing alterations in the LXRα coding region are not included in the basis of the rejection. However, it is noted that claims 1 and 2 encompass more than a simply genetic alteration of the LXRα allele. With respect to the claims encompassing a dominant negative mutation in the LXRα, Examiner agrees that this would be one non-enabled embodiment, but the claims also encompass genetic alterations in any other gene which would affect the LXRα allele. The present claims do not indicate any specific nature of the LXRα allele, *i.e.* altered, absent or disrupted, or any other gene in the genome, only reciting a functional phenotype of the transgenic mouse. The types of alterations encompassed by the present claims include any potential alteration, genetic or physiological, which affects the ability of the mouse to respond to dietary cholesterol, however the instant specification only provides the necessary guidance for the disruption of the LXRα coding sequences. As noted in the basis of the previous rejection, and as summarized in Applicants' traversal, Examiner agrees with Applicant that various mutations or alterations of the LXRα coding sequence which result in a nonfunctional LXRα polypeptide wherein said animal lacks the capacity to respond to dietary cholesterol would be obvious and enabled over the specific example disclosed in the working example in the instant specification. However, the claims 1 and 2 as presently amended encompass more than mutations or alterations in the endogenous LXRα allele and encompass alterations to any gene which may result in the phenotype of not responding to dietary cholesterol. The alterations encompassed by the claims include alteration which affect the LXRα gene indirectly, such as

increasing or decreasing transcription factors, and alterations in other genes which affect cholesterol absorption or cholesterol metabolism. Finally, as specifically recited in claims 12-14, the claims also encompass altering the promoter region of the LXRα gene.

In the basis of the previous rejection, it was set forth that LXRα is part of a large superfamily, whose expression and affect is still not completely understood. Focusing on related family members Manglelsdorf *et al.* describes the nuclear superfamily as over 150 different proteins with a complex array of extracellular signals and transcriptional responses (page 841; first paragraph). While the review means to stress the commonalities among various signaling pathways and that 'it is possible to consider each receptor or each hormone in isolation and to extract common themes, body physiology is rarely so simple' (page 847; bottom of column 2) and concludes that while 'the advances of the last 10 years can be viewed with satisfaction, there is still a long and challenging journey ahead' (page 484; final line). With respect to simply altering a promoter of one of the genes of this family to arrive at a desired phenotype Evans and Beato *et al.* teach that 'recent developments shows that the controls of gene expression by steroid hormones is far more complex than was apparent at the time when the genes for SHRs were isolated. Similar to Manglelsdorf *et al.*, Evans and Beato *et al.* conclude that with more and more players getting on stage, we realize not only this complexity but also the persuasive role steroid hormones play in a vast number of physiological and pathological precesses (Beato pages 855-6; bridging paragraph). Essentially, at the time of filing of the present application, LXRs represented a growing number of superfamily members with increasingly more complex

function, particularly when extended to *in vivo* physiology. The present application has defined a novel function for the LXRα *in vivo* using transgenic mice with a disrupted allele, however, the specification of the present application, nor the art of record, has resolved the many complexities of the role of this receptor in all animals, nor has it resolved the role of this molecule for use in full the scope recited in the claims. Since the applicants have not disclosed all the nucleic acids encompassed by the claims, there is no way to predict efficiency, expression or affect of a particular alteration of a the LXRα gene or the expression of another transgene which may affect the LXRα gene. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03), and this is particularly true in the field of transgenics and transgene behavior. Though the methodology of producing transgenic mice is becoming routine, the result of the genetic alteration can not be predicted.

With respect to the method claims, these claims are included in the basis of the rejection because they require the generation and use of a transgenic mouse as encompassed by the broad independent claims. In particular, due to the unpredictability of transgene behavior and resulting animal phenotype, one of skill in the art would not know what cholesterol-related or bile acid-related phenotypes to monitor. Further, due to the unpredictability of transgene behavior, it is not clear that any transgenic mouse other that one having a disrupted LXRα coding sequence resulting in a null mutation or a nun-functional LXRα polypeptide would have a phenotype which could be consistent with that disclosed in the working examples and which could be used to study the effects on cholesterol or bile acid related metabolism.

Thus, in view of the of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would have required undue experimentation by one of skill to practice the invention as claimed, and therefore, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4-14, 21, 23-27, 29, 44 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 1, 2, 21, 26, 27, 44 and 45 are unclear in the recitation of 'cannot express LXRα sufficient to provide the capacity to respond to dietary cholesterol'. First, it is noted that the claims have been amended to obviate the basis of the previous rejection. With respect to the pending claims, the claims are indefinite because the metes and bounds of sufficient capacity and the levels of dietary cholesterol are not clearly defined in the claims or in light of the teachings of the present specification. First, the claims are unclear because the amount of cholesterol contemplated as being a dietary amount is not clearly set forth. In this case, the amount of cholesterol in circulation depends on consumption and cholesterol metabolism, and it is unclear if the claims encompass only normal levels or also encompass extremely low or extremely high

levels of cholesterol. Second, with respect to a sufficient response to cholesterol, it is unclear what specific response or what level of response is contemplated. It is unclear if the response is only reflected in the LXRα gene expression and affect of an altered LXRα polypeptide, or to any possible response of any gene which can be measured. The specific "capacity" being measured is not clearly set forth therefore, the metes and bounds of the claims are indefinite because what is encompassed by sufficient can not be fairly determined. Dependent claims 4-14, 23-25 and 29 are include in this rejection because they fail to clarify the basis of the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 2, 4-9, 14, 21, 23-27, 29, 44 and 45 rejected under 35 U.S.C. 102(a) as being clearly anticipated by Peet *et al.* (Cell 93:693-704; C45 in IDS) is withdrawn.

Applicants point out that due to the amendment to the inventorship under 37 CFR 1.48(a), the only difference between the inventorship of the instant specification and the authorship of the Peet *et al.* paper is the inclusion of Ma, Janowksi and Hammer as coauthors. Applicants argue that in light of the Declaration of Dr. Mangelsdorf explaining that Ma, Janowksi and Hammer did not contribute to the conception of the subject matter included in Peet

et al. paper and instantly claimed, the Peet et al. paper is not 'by another' and does not qualify as prior art under 102(a). See Applicants amendment, pages 9-10. Applicants' arguments have been fully considered and found persuasive.

As indicated above, the inventorship of the instant application has been changed and Joyce J. Repa has been excludes as an inventor. Further, the Declaration of Dr. Mangelsdorf lists Daniel J. Peet and Jean-Marc A. Lobaccaro as contributing to the inventive concept of the invention instantly claimed. Thus, because the inventorship of the instant application and the authors of the Peet *et al.* are the same, the teachings in Peet *et al.* does not represent the teachings by another.

Conclusion

No claim is allowed. Claims 4-9 are objected because they are dependent on rejected claims, however would be found allowable if rewritten in independent form including the embodiments of the independent claims. All the claims are free of the prior art of record because the prior art of record fails to teach or suggest the disruption of the promoter region of the LXRα gene with an inducible/repressible promoter. However, the claims are subject to other rejections.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

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